Clinico-pathological Predictors of Mismatch Repair Deficiency in Sebaceous Neoplasia: A Large Case Series from a Single Australian Private Pathology Service

Michael D. Walsh, PhD¹, Harindra Jayasekara, MD, PhD^{2,3,4,5}, Alvin Huang, BBmed^{2,4},
Ingrid M. Winship, MD^{6,7}¥, Daniel D. Buchanan, PhD^{2,4,6}¥

¹ Sullivan Nicolaides Pathology, Bowen Hills, Queensland, Australia

² Colorectal Oncogenomics Group, Department of Clinical Pathology, The University of Melbourne, Parkville, Victoria, Australia

³ Cancer Epidemiology and Intelligence Division, Cancer Council Victoria, St Kilda, Melbourne, Victoria, Australia

⁴ University of Melbourne Centre for Cancer Research, Victorian Comprehensive Cancer Centre, Parkville, Victoria, Australia

⁵ Centre for Alcohol Policy Research, La Trobe University, Melbourne, Victoria, Australia

⁶ Genomic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Parkville, Australia

⁷ Department of Medicine, The University of Melbourne, Parkville, Victoria, Australia

¥ These authors contributed equally

Short Title: Mismatch repair in sebaceous neoplasia

Corresponding Author:

Associate Professor Daniel Buchanan

Colorectal Oncogenomics Group

Department of Clinical Pathology

The University of Melbourne

Victorian Comprehensive Cancer Centre

305 Grattan Street

Parkville, Victoria, 3010 Australia

Ph: +61 385597004

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ajd.12958](https://doi.org/10.1111/ajd.12958)

This article is protected by copyright. All rights reserved

Email: daniel.buchanan@unimelb.edu.au

Acknowledgments: We are indebted to Drs Mark Clendenning, Jihoon (Eric) Joo, Bernard Pope, Khalid Mahmood, and Mr Neil O'Callaghan, Ms Sharelle Joseland, Ms Susan Preston and Mr Thomas Green from the Colorectal Oncogenomics Group for their support for this manuscript. We are indebted to Ms Kirsty Storey and Ms Jessica Taylor from the Genomic Medicine and Family Cancer Clinic for their support of this manuscript.

Financial Disclosure: Dr Buchanan served as consultants on the Tumour Agnostic (dMMR) Advisory Board of Merck Sharp and Dohme in 2017 for Pembrolizumab.

Funding/Support: This study was supported in part by a National Health and Medical Research Council of Australia (NHMRC) project grant 1108797 (PI- Ingrid Winship), by a NHMRC R.D. Wright Career Development Fellowship for Dr Buchanan and by Victorian Cancer Agency Early Career Seed grant for Dr Jayasekara. Funding supported the design and conduct of the study, collection, management, analysis and interpretation of data.

Manuscript word count: 2999

Tables: four

Figures: one

Article type : Original Research

Title: Clinico-pathological Predictors of Mismatch Repair Deficiency in Sebaceous Neoplasia: A Large Case Series from a Single Australian Private Pathology Service

Abstract

Background/Objectives: Loss of expression of mismatch repair (MMR) proteins is frequently observed in sebaceous skin lesions and can be a herald for Lynch syndrome. The aim of this study was to identify clinico-pathological predictors of MMR-deficiency in sebaceous neoplasia that could aid dermatologists and pathologists in determining which sebaceous lesions should undergo MMR immunohistochemistry.

Methods: An audit of sebaceous skin lesions (excluding hyperplasia) where pathologist-initiated MMR IHC was performed between January 2009 to December 2016 was undertaken from a single pathology practice identifying 928 lesions from 882 individuals. Lesions were further analysed for differences in gender, age at diagnosis, lesion type and anatomic location, stratified by MMR status.

Results: The 882 individuals (67.7% male) had a mean age of diagnosis of 68.4 years $\pm$ SD=13.3 years. Nearly two-thirds of the lesions were sebaceous adenomas, with 82.6% of all lesions occurring on the head and neck. MMR-deficiency, observed in 282 of the 919 lesions (30.7%), was most common in sebaceous adenomas (210/282; 74.5%). MMR-deficient lesions occurred predominantly on the trunk or limbs (64.7%), compared with 23.2% in head or neck ($p<0.001$). Loss of MSH2 and MSH6 protein expression was most frequent pattern of loss (187/281; 66.5%). The highest AUC for discriminating MMR-deficient sebaceous lesions from MMR-proficient lesions was observed for the ROC curve based on subgroups defined by type and anatomic location of the sebaceous lesion (AUC=0.68).

Conclusion: The best combination of measured clinico-pathological features achieved only modest positive predictive values, sensitivity and specificity for identifying MMR-deficient sebaceous skin lesions.

Key words: Sebaceous adenoma, sebaceoma, sebaceous carcinoma, mismatch repair deficiency, Muir-Torre syndrome, Lynch syndrome, mismatch repair immunohistochemistry.

Learning Points

- To date, most studies of the clinico-pathological factors associated with MMR-deficiency in sebaceous skin lesions have been small and the findings have been inconsistent.
- In this the largest study of sebaceous skin lesions performed to date, commonly collected clinico-pathological features were not shown to be strong predictors for who and which sebaceous lesions should be tested for the presence of MMR-deficiency.

Introduction

Sebaceous neoplasms describe rare skin tumours involving the sebaceous glands that include sebaceous adenomas, sebaceous carcinomas and sebaceomas (collectively referred to as sebaceous neoplasia in this study) which is in contrast to sebaceous gland hyperplasia which is a more frequently occurring lesion, particularly in sun-exposed skin (reviewed in ¹). The incidence rate of sebaceous carcinomas is estimated to be 1 per 1,000,000 patient years ^{2,3}. Risk factors for the sebaceous neoplasia include a history of irradiation, immunosuppression, familial retinoblastoma and Muir-Torre syndrome (MTS)⁴. In 1967, Muir et al. ⁵ and in 1968, Torre ⁶ independently reported a condition where individuals had multiple sebaceous lesions and internal (non-cutaneous) malignancies. MTS was later shown to be a phenotypic variant of Lynch syndrome ⁷, an autosomal dominantly inherited cancer predisposition caused by germline mutations in the DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2).

Carriers of a germline MMR gene mutation (Lynch syndrome) have an increased risk of developing different cancers including cancer of the colon and rectum (CRC), and endometrium, among others ⁸. Therefore, the identification of MMR gene mutation carriers is of critical importance for cancer prevention and early detection. The characteristic features of tumours arising in Lynch syndrome carriers is widespread DNA replication errors occurring within microsatellite repeats (otherwise known as microsatellite instability (MSI-H)) and loss of expression of one or more of the MMR proteins determined by immunohistochemical staining (IHC), collectively referred to as tumour MMR-deficiency. Sebaceous neoplasia in individuals carrying germline MMR

gene mutations also demonstrate MMR-deficiency⁹; and as such MMR IHC screening of sebaceous lesions for evidence of MMR-deficiency offers opportunities for carrier identification and cancer prevention.

MMR IHC testing of sebaceous neoplasia for MMR-deficiency has been reported to be a sensitive screening tool for identifying MMR gene mutation carriers¹⁰, generating support for MMR IHC testing of all sebaceous neoplasia for MMR-deficiency (universal testing)¹¹, however, several limitations are evident, namely (i) reports that only 31% - 44% of sebaceous neoplasms demonstrate MMR-deficiency^{11,12} and (ii) that MMR-deficiency in a sebaceous neoplasm is not diagnostic of a germline MMR gene mutation^{10,13,14}. Several studies have attempted to associate clinico-pathological factors with MMR-deficiency in sebaceous lesions including evidence for a younger age at diagnosis of sebaceous neoplasm, predominance of sebaceous adenoma tumour type and involvement of sites outside of the head and neck region; the majority of these studies have been small and their findings have often been conflicting^{9-11 15-17}. Determining which sebaceous neoplasms should be tested for MMR-deficiency (in the absence of previous or concurrent internal malignancy) in order to identify patients carrying a germline MMR gene mutation currently presents a significant challenge for dermatologists/pathologists/clinicians.

In this study, we report on a large series of sebaceous skin lesions tested for MMR-deficiency derived from a single private pathology practice in Brisbane, Australia. We investigated features, alone and in combination, including age at diagnosis, sex, lesion type, and site on the body, that may differentiate MMR-deficient lesions from those that are MMR-proficient in order to better guide future MMR IHC screening and the subsequent identification of germline MMR mutation carriers.

Methods

An audit was performed to identify all cases of sebaceous skin lesions which MMR IHC was performed as a reflex request (i.e. pathologist-initiated) between January 2009 and December 2016 derived from Sullivan Nicolaides Pathology, a private pathology practice in Brisbane, Australia (catchment encompassing ~5 million people in north-eastern Australia). A search of all histopathology reports containing the keyword “sebaceo*” was used at SNP to determine the proportion of each sebaceous tumour classification for which reflex MMR IHC was requested. Sebaceous hyperplasia were excluded from this study. The study was approved by Sullivan Nicolaides Pathology with consent waived due to 1) absence of contact to patients, 2) no use of patient identifiers and 3) no use of biospecimens.

This article is protected by copyright. All rights reserved

Statistical analysis

Basic demographic and tumor characteristics of individuals with sebaceous neoplasia were assessed descriptively. The relationship between MMR status and sex, type of sebaceous lesion (sebaceous adenoma/sebaceoma versus sebaceous carcinoma), and anatomic location (head/neck versus trunk/limbs) for eligible sebaceous neoplasms was assessed using the χ^2 test. Student's t-test was used to compare mean age at diagnosis by MMR status. We also assessed sex, mean age at diagnosis, subtype of sebaceous neoplasia and anatomic location for MMR-deficient sebaceous neoplasms by the pattern of immunohistochemistry loss, using ANOVA test to compare mean age and χ^2 test to compare others. We assessed sensitivity, specificity, positive and negative predictive values, and likelihood ratio for subgroups, defined by sex, age at diagnosis, subtype of sebaceous neoplasia and anatomic location, for predicting MMR-deficiency. By definition, sensitivity is the probability of a value above a threshold among those with disease (i.e., MMR-deficient) while specificity is the probability of a value below a threshold among those without disease (i.e., MMR-proficient). The positive predictive value is the probability that a lesion above a threshold is truly MMR-deficient while the negative predictive value is the probability that a lesion below a threshold is truly MMR-proficient. The likelihood ratio compares the probability of getting a value above a threshold if the lesion was MMR-deficient with the corresponding probability if the lesion was MMR-proficient [=sensitivity/(1-specificity)]. Confidence intervals (CI) for sensitivities, specificities, predictive values and likelihood ratios were calculated using the binomial formula. The Receiver Operating Characteristic (ROC) curve, used to discriminate among MMR-deficient or MMR-proficient sebaceous neoplasms for subgroups defined according to combined sex, age, type and anatomic location, arranged in an ordinal scale (low- to high-risk), was plotted as 1 minus the specificity (i.e., the false-positive rate) versus sensitivity¹⁸. The area under the ROC curve (AUC) is equivalent to the probability that the predicted risk is higher for a MMR-deficient lesion than for a MMR-proficient lesion¹⁸. All analyses were two-sided, and significance was set at a p value of 0.05. All statistical analyses were performed using Stata 15.0 (StataCorp, College Station, TX).

Results

Within the audit period, MMR IHC was performed on 928 lesions obtained from 882 individuals, with a mean age at first diagnosis of sebaceous neoplasia of 68.4 years $\pm$ SD=13.3 years and over two-thirds from males (**Table 1**). Nearly two-thirds of the lesions were sebaceous adenomas and 82.6% occurred in the head and neck regions (**Table 1**). Thirty-one individuals had multiple lesions tested during the ascertainment period (**Table 1** and **Supplementary Table 1**).

Rare lesions with regions of sebaceous differentiation were also included (**Table 1** and **Supplementary Table 2**).

Sebaceous neoplasia was further characterised for differences in gender, age at diagnosis, lesion type and anatomic location, stratified by MMR status (**Table 2**). MMR-deficiency was reported in 282 of the 919 lesions tested (30.7%). MMR-deficiency was most common in sebaceous adenomas (210/594; 35.4%), followed by sebaceoma (34/141; 24.1%) and sebaceous carcinomas (34/150; 22.7%); basal cell carcinoma and squamous cell carcinomas with focal sebaceous differentiation exhibited lower proportions of MMR-deficiency (11.1% and 7.7%, respectively). Approximately two-thirds of the sebaceous adenomas, sebaceomas and sebaceous carcinomas combined on the trunk or limbs were MMR-deficient compared with only 23.2% of lesions in head or neck ($p<0.001$; **Table 2**). This was most pronounced for sebaceomas with all but two of the 19 sebaceomas from the trunk and limb location demonstrating MMR-deficiency (89.5%) compared with only 14% in the Head/Neck location (Further stratification of the sebaceous lesion type according to anatomical subtype is provided in **Supplementary Table 3**). There were no statistical differences observed in the distribution of all lesions by MMR status for gender or mean age at diagnosis. Considering age at diagnosis in 10-year age brackets, the highest frequency of MMR-deficiency for sebaceous adenomas, sebaceomas and sebaceous carcinomas was observed in those diagnosed between 60-69 years with 28.1%, 38.2% and 26.5%, respectively (**Supplementary Table 4**). Early presentation of sebaceous lesions was not associated with MMR-deficiency with 10.4% of the MMR-deficient and 10.1% of MMR-proficient sebaceous lesions detected in those diagnosed under 50 years of age (**Supplementary Table 4**).

Loss of MSH2 and MSH6 protein expression was the most frequent pattern within the MMR-deficient sebaceous lesions (187/281; 66.5%, **Table 3**). There was evidence that age at diagnosis differed by pattern of protein loss in the MMR-deficient sebaceous lesions ($p=0.04$) with lesions with solitary loss of MSH6 (30/281; 10.7%) occurring, on average, at an older age to those with MLH1/PMS2 or MSH2/MSH6 loss (**Table 3**). Seventy-two percent of the MMR-deficient lesions in the head and neck region showed loss of MSH2/MSH6 protein expression (**Table 3**). Out of the 31 individuals who had two or more sebaceous lesions (total of 77 lesions) available for analysis (**Supplementary Table 1**), concordance of MMR protein expression was observed for 27 individuals (87%; 14 concordant for MMR-deficiency and 13 for MMR-proficiency). The remaining 4 individuals with multiple lesions tested demonstrated discordant MMR IHC results; one individual had a MMR-proficient sebaceous adenoma aged 45 years then five subsequent

sebaceous adenomas between 46 and 48 years of age all demonstrating loss of MSH2/MSH6 expression (**Supplementary Table 1**).

The highest AUC for discriminating MMR-deficient sebaceous lesions from MMR-proficient lesions was observed for the ROC curve based on subgroups defined by type and anatomic location of the sebaceous lesion (AUC=0.6834; **Figure 1**). All other ROC curves and AUCs for subgroups defined by sex, age, type and anatomic location are shown in **Supplementary Figure 1**. Sensitivities, specificities, positive and negative predictive values, and likelihood ratios for the prediction of MMR-deficient sebaceous lesions are shown in **Table 4**. The highest sensitivity for identifying a MMR-deficient sebaceous lesion was provided by testing males with sebaceous adenomas or sebaceomas (63.2, 95% CI=57.2-68.9), while the highest specificity was achieved by a combination of all features (Male with diagnosis age <70 years with sebaceous adenoma/sebaceoma in head/neck (74.3, 95% CI=70.6-77.7). Compared with all others, the combined clinical characteristics of age at diagnosis of <70 years with sebaceous adenoma or sebaceoma subtype achieved the highest positive predictive value of 37.3 (95% CI: 32.5-42.3) and highest negative predictive value of 73.2 (95% CI: 69.1-77.1) which resulted in the highest likelihood ratio=1.30 (95% CI: 1.12-1.50) with corresponding sensitivity of 52.7 (95% CI: 46.6-58.7) and specificity of 59.4 (95% CI: 55.3-63.3). The next best approach resulted from the combination of testing males diagnosed <70 years of age (**Table 4**).

Discussion

MTS is a subtype of Lynch syndrome defined by the occurrence of synchronous or metachronous sebaceous neoplasia and one Lynch Syndrome-related internal cancer, irrespective of family history or age at onset where, similar to the internal cancers, sebaceous lesions are characterised by the presence of tumour MMR-deficiency. Sebaceous neoplasia may precede the development of the internal cancers in MTS¹⁴, highlighting the importance of screening these lesions for MMR-deficiency and the opportunity for internal cancer prevention strategies. In this study, MMR-deficiency was observed in 30.7% of 919 sebaceous lesions tested, with a predominance for lesions on the trunk or limbs to show loss of MMR protein expression, two-thirds of which was loss of MSH2 and MSH6 protein expression. The ROC curve demonstrated only moderate prediction of MMR-deficiency for the best combination of clinico-pathological features (sebaceous lesion type and anatomical site), with an AUC of 0.6834. The combined clinical characteristics of age at diagnosis of <70 years with sebaceous adenoma or sebaceoma subtype

achieved the highest positive and negative predictive values with a likelihood ratio for MMR-deficiency of 1.30 (95% CI: 1.12-1.50).

Previous studies investigating MMR-deficiency in sebaceous neoplasia have reported frequencies ranging from 25% and 66% (reviewed in Lee et al,¹⁹) although several studies included patients with a priori high-risk for MTS recruited from genetics clinics, likely upwardly biasing the frequency of MMR-deficiency^{10,14}. Our frequency of MMR-deficiency (30.7%) is similar to that reported by Cesinaro et al.2007 (18/70; 25.7%)⁹, a study cohort comprised of patients with isolated sebaceous neoplasms and those with both sebaceous neoplasms and extra-cutaneous cancer. Across studies, loss of MSH2 protein expression (and its heterodimer partner MSH6) is the most frequently described pattern of IHC loss in sebaceous neoplasia^{9,16} and was the dominant pattern of MMR protein loss in our study (66.5%). Further consistency in findings between our study and with previous studies was observed for lesion type with sebaceous adenomas the most frequent sebaceous neoplasm demonstrating MMR-deficiency¹⁶.

We note that a large majority of sebaceous lesions (81%) were from the head or neck, consistent with a higher density of sebaceous glands on the upper body, especially the face²⁰. Lesions on the trunk or limbs, compared with the head or neck, were significantly more likely to exhibit MMR-deficiency in our study (64.7% v 23.2%; $p<0.001$). These results concur with previous studies by Singh et al. 2008, Roberts et al. 2013¹⁵ and Jessup et al. 2016¹⁶, suggesting that the increased UV exposure to head and neck contributes to the development of MMR-proficient sebaceous neoplasia.²¹

The clinical utility of MMR IHC testing in CRC and endometrial cancer for identifying Lynch syndrome has led to the recommendation of universal or reflex IHC of all newly diagnosed CRCs for MMR protein status, endorsed as the preferred approach to identify Lynch syndrome²²⁻²⁴. By contrast, no guidelines or recommendations exist for MMR IHC testing of sebaceous neoplasia for the identification of germline MMR gene mutation carriers (MTS-Lynch syndrome). This is perhaps due to the limitations of studies published to date of small sample sizes, or, like ours, unable to assess germline mutation status to determine true effectiveness of MMR IHC for identifying MTS-Lynch. Furthermore, recent studies have shown that a germline MMR gene mutation is identified in less than half of the individuals with MMR-deficient sebaceous neoplasia^{10,14}. This is further complicated by reports that a small number of individuals have a pattern of MMR protein loss by IHC that is not consistent with the MMR gene harbouring the underlying germline mutation^{14,15}. Despite these current limitations, MMR IHC testing to identify MMR-

deficiency is currently the only useful screening tool for identifying MTS-Lynch but is not diagnostic for MMR gene mutation.

Of interest, 87% of individuals with multiple sebaceous lesions in this study demonstrated concordant results for MMR protein expression with roughly equal proportions showing either all lesions with MMR-deficiency or all with MMR-proficiency. This raises two important points namely; MMR IHC testing of multiple lesions from an individual can be informative as to a common aetiology but also that the presence of multiple sebaceous lesions is not predictor of MMR-deficiency. Multiplicity of sebaceous lesions has been suggested as an important predictor of MTS-Lynch, as indicated by odds ratio of 51.95 (95%CI 6.52-414) for association with MTS in the study by Roberts et al,¹⁴, where it was given twice the weight compared with other factors in their Mayo MTS risk algorithm¹⁴.

This study has several limitations. We could not determine sufficiently whether the audited individuals with sebaceous lesions were diagnosed with another non-cutaneous cancer. A personal history of non-cutaneous, Lynch-related cancer in an individual presenting with sebaceous neoplasm is strongly associated with MTS-Lynch¹⁴. Similarly, we did not have information on family history of cancer as this has been shown to also be strongly associated with MTS-Lynch¹⁴. In addition, the scope of the study did not allow testing for germline MMR gene mutations in people with MMR-deficient sebaceous lesions. Previous studies have shown that MMR IHC testing of sebaceous lesions has poor sensitivity and specificity for identifying germline MMR gene mutations. We note that Everett et al. 2007 (17), who completed germline screening on MMR IHC deficient sebaceous neoplasms, observed germline MMR mutations in only 14/38; 36.8%, of patients, highlighting that MMR protein IHC in sebaceous lesions is not necessarily diagnostic for Lynch Syndrome. In the absence of further genetic and tumour characterisation we cannot discriminate between the clinically important subgroups that are known to exist within tumours with MMR-deficiency namely; (i) Lynch syndrome, (ii) MLH1 methylation positive lesions with corresponding loss of MLH1/PMS2 expression and (iii) the group referred to as having Suspected Lynch syndrome with an absence of both germline MMR gene mutation or tumour MLH1 methylation, a group also observed in CRC and endometrial cancer²⁵.

The challenge remains for clinicians and pathologists to determine which sebaceous skin lesions should be tested for MMR-deficiency. This study, the largest of its kind shows that the best combination of measured clinico-pathological features achieved only modest positive predictive values, sensitivity and specificity for identifying MMR-deficient sebaceous skin lesions. Further

genotype-phenotype correlation in sebaceous neoplasia is essential to improve decision making for MMR testing and its clinical consequences.

References

1. Flux K. Sebaceous Neoplasms. *Surgical pathology clinics*. 2017;10(2):367-382.
2. Dasgupta T, Wilson LD, Yu JB. A retrospective review of 1349 cases of sebaceous carcinoma. *Cancer*. 2009;115(1):158-165.
3. Dores GM, Curtis RE, Toro JR, Devesa SS, Fraumeni JF, Jr. Incidence of cutaneous sebaceous carcinoma and risk of associated neoplasms: insight into Muir-Torre syndrome. *Cancer*. 2008;113(12):3372-3381.
4. Kyllö RL, Brady KL, Hurst EA. Sebaceous carcinoma: review of the literature. *Dermatologic surgery* : official publication for American Society for Dermatologic Surgery [et al]. 2015;41(1):1-15.
5. Muir EG, Bell AJ, Barlow KA. Multiple primary carcinomata of the colon, duodenum, and larynx associated with kerato-acanthomata of the face. *Br J Surg*. 1967;54(3):191-195.
6. Torre D. Multiple sebaceous tumors. *Arch Dermatol*. 1968;98(5):549-551.
7. Lynch HT, Lynch PM, Pester J, Fusaro RM. The cancer family syndrome. Rare cutaneous phenotypic linkage of Torre's syndrome. *Arch Intern Med*. 1981;141(5):607-611.
8. Win AK, Young JP, Lindor NM, et al. Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. *J Clin Oncol*. 2012;30(9):958-964.
9. Cesinaro AM, Ubiali A, Sighinolfi P, Trentini GP, Gentili F, Facchetti F. Mismatch repair proteins expression and microsatellite instability in skin lesions with sebaceous differentiation: a study in different clinical subgroups with and without extracutaneous cancer. *Am J Dermatopathol*. 2007;29(4):351-358.
10. Everett JN, Raymond VM, Dandapani M, et al. Screening for germline mismatch repair mutations following diagnosis of sebaceous neoplasm. *JAMA Dermatol*. 2014;150(12):1315-1321.
11. Orta L, Klimstra DS, Qin J, et al. Towards identification of hereditary DNA mismatch repair deficiency: sebaceous neoplasm warrants routine immunohistochemical screening regardless of patient's age or other clinical characteristics. *Am J Surg Pathol*. 2009;33(6):934-944.

12. Lamba AR, Moore AY, Moore T, Rhees J, Arnold MA, Boland CR. Defective DNA mismatch repair activity is common in sebaceous neoplasms, and may be an ineffective approach to screen for Lynch syndrome. *Fam Cancer*. 2015;14(2):259-264.
13. Ponti G, Pellacani G, Ruini C, et al. Muir-Torre syndrome or phenocopy? The value of the immunohistochemical expression of mismatch repair proteins in sebaceous tumors of immunocompromised patients. *Fam Cancer*. 2014;13(4):553-561.
14. Roberts ME, Riegert-Johnson DL, Thomas BC, et al. A clinical scoring system to identify patients with sebaceous neoplasms at risk for the Muir-Torre variant of Lynch syndrome. *Genet Med*. 2014;16(9):711-716.
15. Roberts ME, Riegert-Johnson DL, Thomas BC, et al. Screening for Muir-Torre syndrome using mismatch repair protein immunohistochemistry of sebaceous neoplasms. *J Genet Couns*. 2013;22(3):393-405.
16. Jessup CJ, Redston M, Tilton E, Reimann JD. Importance of universal mismatch repair protein immunohistochemistry in patients with sebaceous neoplasia as an initial screening tool for Muir-Torre syndrome. *Hum Pathol*. 2016;49:1-9.
17. Kruse R, Rutten A, Schweiger N, et al. Frequency of microsatellite instability in unselected sebaceous gland neoplasias and hyperplasias. *J Invest Dermatol*. 2003;120(5):858-864.
18. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143(1):29-36.
19. Lee JB, Litzner BR, Vidal CI. Review of the current medical literature and assessment of current utilization patterns regarding mismatch repair protein immunohistochemistry in cutaneous Muir-Torre syndrome-associated neoplasms. *J Cutan Pathol*. 2017;44(11):931-937.
20. Smith KR, Thiboutot DM. Thematic review series: skin lipids. Sebaceous gland lipids: friend or foe? *J Lipid Res*. 2008;49(2):271-281.
21. Pfeifer GP, You YH, Besaratinia A. Mutations induced by ultraviolet light. *Mutat Res*. 2005;571(1-2):19-31.
22. Evaluation of Genomic Applications in P, Prevention Working G. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genet Med*. 2009;11(1):35-41.
23. Giardiello FM, Allen JJ, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. *Am J Gastroenterol*. 2014;109(8):1159-1179.

24. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. *J Clin Oncol*. 2015;33(2):209-217.
25. Buchanan DD, Rosty C, Clendenning M, Spurdle AB, Win AK. Clinical problems of colorectal cancer and endometrial cancer cases with unknown cause of tumor mismatch repair deficiency (suspected Lynch syndrome). The application of clinical genetics. 2014;7:183-193.

Figures

Figure 1. Receiver operating characteristic curve (ROC) for clinical characteristic prediction of mismatch repair-deficient sebaceous skin lesions - Clinical characteristic were used to define the following subgroups: sebaceous carcinoma in trunk/limbs, sebaceous carcinoma in head/neck, sebaceous adenoma/sebaceoma in trunk/limbs, sebaceous adenoma/sebaceoma in head/neck. AUC, area under the ROC curve; se, standard error.

Table 1. Descriptive characteristics for individuals with sebaceous neoplasia

Characteristic	Individuals (N=882)
Sex, n (%)	
Male	597 (67.7)
Female	285 (32.3)
Age at diagnosis (years)	
Mean (SD)	68.4 (13.3)
Range	16.1-100.1
Total number of sebaceous skin lesions	928
Number of individuals with >1 sebaceous skin lesion, n (%)	31 (3.5) 24 individuals with 2 lesions 3 individuals with 3 lesions 1 individual with 4 lesions 2 individuals with 5 lesions 1 individual with 6 lesions
Type of sebaceous skin lesion, n (%)	
Sebaceous adenoma	566 (64.2)
Sebaceoma	127 (14.4)
Sebaceous carcinoma	147 (16.7)
BCC + Sebaceous differentiation	18 (2.0)
SCC + Sebaceous differentiation	13 (1.5)
Miscellaneous/other	11 (1.2)
IEC with sebaceous differentiation	3
Sebocrine adenoma	3
Adnexal tumour with sebaceous differentiation	1
Appendageal carcinoma	1
Mixed appendageal tumour	1
Sebaceous carcinoma (metastatic)	1
Sebaceous trichoepithelioma	1
Location, n (%)	
Head/Neck	728 (82.6)
Trunk	108 (12.2)
Limbs	40 (4.5)
Unknown	6 (0.7)

SD, standard deviation; BCC, Basal cell carcinoma; SCC, squamous cell carcinoma; IEC, intra-epithelial carcinoma.

Table 2. Comparison of sebaceous skin lesions by mismatch repair status

Characteristic	All lesions (n=919*)	MMR-deficient (n=282)	MMR-proficient (n=637)	P value ^a
Sex, n (%)				
Male	623 (100)	199 (31.9)	424 (68.1)	0.2
Female	296 (100)	83 (28.0)	213 (72.0)	
Age at diagnosis (years)				
Mean (SD)	68.2 (13.4)	67.7 (13.0)	68.4 (13.6)	0.5
Type of sebaceous skin lesion, n (%)				
Sebaceous adenoma	594 (100)	210 (35.4)	384 (64.6)	0.01 ^b
Sebaceoma	141 (100)	34 (24.1)	107 (75.9)	
Sebaceous carcinoma	150 (100)	34 (22.7)	116 (77.3)	
BCC + Sebaceous differentiation	18 (100)	2 (11.1)	16 (88.9)	
SCC + Sebaceous differentiation	13 (100)	1 (7.7)	12 (92.3)	
Miscellaneous/other	3 (100)	1 (33.3)	2 (66.7)	
Location, n (%)				
Head/neck	747 (100)	173 (23.2)	574 (76.8)	<0.001 ^c
Trunk/limbs	167 (100)	108 (64.7)	59 (35.3)	
Unknown	5 (100)	1 (20.0)	4 (80.0)	

SD, standard deviation; MMR, mismatch repair; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

* n=9 out of n=928 sebaceous skin lesions were deemed ineligible for this analysis.

^a χ^2 tests except for age where t test was used.

^b Comparing sebaceous adenoma plus sebaceoma versus sebaceous carcinoma by MMR status.

^c Excluding unknown location.

Table 3. Comparison of mismatch repair-deficient sebaceous skin lesions by the pattern of immunohistochemistry loss

Characteristic	All lesions (281*)	MLH1/PMS2 (n=60, 21.4%)	MSH2/MSH6 (n=187, 66.5%)	MSH6 (n=30, 10.7%)	PMS2 (n=4, 1.4%)	P value ^a
Sex, n (%)						
Male	198 (100)	37 (18.7)	139 (70.2)	20 (10.1)	2 (1.0)	0.1
Female	83 (100)	23 (27.7)	48 (57.8)	10 (12.1)	2 (2.4)	
Age at diagnosis (years)						
Mean (SD)	67.7 (13.0)	66.3 (14.1)	67.2 (12.8)	73.3 (10.0)	71.8 (17.5)	0.04
Type of sebaceous skin lesion, n (%)						
Sebaceous adenoma	209 (100)	46 (22.0)	137 (65.6)	22 (10.5)	4 (1.9)	Not calculated
Sebaceoma	34 (100)	7 (20.6)	24 (70.6)	3 (8.8)	-	
Sebaceous carcinoma	34 (100)	6 (17.6)	25 (73.5)	3 (8.8)	-	
BCC + Sebaceous differentiation	2 (100)	-	1 (50.0)	1 (50.0)	-	
SCC + Sebaceous differentiation	1 (100)	-	-	1 (100)	-	
Miscellaneous/other	1 (100)	1 (100)	-	-	-	
Location, n (%)						
Head/neck	172 (100)	31 (18.0)	124 (72.1)	13 (7.6)	4 (2.3)	0.01 ^b
Trunk/limbs	108 (100)	29 (26.9)	62 (57.4)	17 (15.7)	-	
Unknown	1 (100)	-	1 (100)	-	-	

SD, standard deviation; BCC, Basal cell carcinoma; SCC, squamous cell carcinoma

* n=1 out of n=282 MMR-deficient sebaceous skin lesions was excluded due to unknown pattern of immunohistochemistry loss.

^a χ^2 tests except for age where ANOVA test was, excluding PMS2.

^b Excluding unknown location.

Table 4. Sensitivity, specificity and predictive value of clinical characteristics for prediction of mismatch repair-deficient sebaceous skin lesions

	Proportion out of all sebaceous skin lesions (N=880) ^a n (%)	Proportion out of MMR- deficient skin lesions (N=277) ^a n (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive value % (95% CI)	Negative predictive value % (95% CI)	Likelihood ratio (95% CI)
Sex							
Male (compared with female)	601 (68.3)	196 (70.8)	70.8 (65.0- 76.0)	32.8 (29.1- 36.7)	32.6 (28.9-36.5)	71.0 (65.3-76.2)	1.05 (0.96- 1.16)
Age at diagnosis							
<70 years (compared with ≥70 years)	452 (51.4)	159 (57.4)	57.4 (51.3- 63.3)	51.4 (47.3- 55.5)	35.2 (30.8-39.8)	72.4 (67.9-76.6)	1.18 (1.04- 1.35)
Type of sebaceous skin lesion							
Sebaceous adenoma/sebaceoma (compared with sebaceous carcinoma)	732 (83.2)	244 (88.1)	88.1 (83.7- 91.7)	19.1 (16.0- 22.4)	33.3 (29.9-36.9)	77.7 (70.1-84.1)	1.09 (1.03- 1.15)
Location							
Head/neck (compared with trunk/limbs)	719 (81.7)	171 (61.7)	61.7 (55.7- 67.5)	9.1 (7.0- 11.7)	23.8 (20.7-27.1)	34.2 (26.9-42.0)	0.68 (0.62- 0.75)
Combined ^b							
Age <70 male	308 (35.0)	114 (41.2)	41.2	67.8	37.0 (31.6-42.7)	71.5 (67.6-75.2)	1.28 (1.07-

			(35.3-47.2)	(63.9-71.5)			1.54)
Male with sebaceous adenoma/sebaceoma	519 (59.0)	175 (63.2)	63.2 (57.2-68.9)	43.0 (39.0-47.0)	33.7 (29.7-38.0)	71.7 (66.8-76.3)	1.11 (0.99-1.24)
Age <70 with sebaceous adenoma/sebaceoma	391 (44.4)	146 (52.7)	52.7 (46.6-58.7)	59.4 (55.3-63.3)	37.3 (32.5-42.3)	73.2 (69.1-77.1)	1.30 (1.12-1.50)
Male with lesions in head/neck	476 (54.1)	114 (41.2)	41.2 (35.3-47.2)	40.0 (36.0-44.0)	23.9 (20.2-28.0)	59.7 (54.7-64.5)	0.69 (0.59-0.80)
Age <70 with lesions in head/neck	360 (40.9)	93 (33.6)	33.6 (28.0-39.5)	55.7 (51.7-59.7)	25.8 (21.4-30.7)	64.6 (60.3-68.7)	0.76 (0.63-0.92)
Sebaceous adenoma/sebaceoma in head/neck	596 (67.7)	149 (53.8)	53.8 (47.7-59.8)	25.9 (22.4-29.6)	25.0 (21.6-28.7)	54.9 (48.9-60.8)	0.73 (0.64-0.82)
Male with sebaceous adenoma/sebaceoma in head/neck	412 (46.8)	101 (36.5)	36.5 (30.8-42.4)	48.4 (44.4-52.5)	24.5 (20.4-29.0)	62.4 (57.8-66.8)	0.71 (0.59-0.84)
Age <70 with sebaceous adenoma/sebaceoma in head/neck	308 (35.0)	85 (30.7)	30.7 (25.3-36.5)	63.0 (59.0-66.9)	27.6 (22.7-33.0)	66.4 (62.4-70.3)	0.83 (0.68-1.02)
Age <70 male with sebaceous adenoma/sebaceoma in head/neck	213 (24.2)	58 (20.9)	20.9 (16.3-26.2)	74.3 (70.6-77.7)	27.2 (21.4-33.7)	67.2 (63.5-70.7)	0.82 (0.62-1.06)

MMR, mismatch repair; CI, confidence interval.

^a Includes eligible sebaceous adenoma, sebaceoma and sebaceous carcinoma only with no missing information on sex, age and location.

^b Compared with all others.

Author Manuscript

ajd_12958_f1.tif

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Walsh, MD;Jayasekara, H;Huang, A;Winship, IM;Buchanan, DD

Title:

Clinico-pathological predictors of mismatch repair deficiency in sebaceous neoplasia: A large case series from a single Australian private pathology service

Date:

2019-05-01

Citation:

Walsh, M. D., Jayasekara, H., Huang, A., Winship, I. M. & Buchanan, D. D. (2019). Clinico-pathological predictors of mismatch repair deficiency in sebaceous neoplasia: A large case series from a single Australian private pathology service. AUSTRALASIAN JOURNAL OF DERMATOLOGY, 60 (2), pp.126-133. <https://doi.org/10.1111/ajd.12958>.

Persistent Link:

<http://hdl.handle.net/11343/284851>